Effects of Lifetime Exercise on the Outcome of In Vitro Fertilization

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OBJECTIVE: To estimate whether exercise before the first cycle of in vitro fertilization (IVF) affects cycle outcomes.

METHODS: A total of 2,232 patients were prospectively enrolled before undergoing their first cycle of IVF for the treatment of infertility from 1994–2003 at three IVF clinics in the greater Boston area. The primary IVF outcomes of interest included successful live birth and four points of cycle failure: cycle cancellation, failed fertilization, implantation failure, and pregnancy loss. Unconditional logistic regression adjusting for observed confounders was used to quantify the relation between self-reported exercise and cycle outcome.

RESULTS: In general, women who reported regular exercise were no more likely to have a live birth compared with those women who did not report exercise (odds ratio [OR] 0.8, 95% confidence interval [CI] 0.7–1.0; $P=.07$). Women who reported exercising 4 hours or more per week for 1–9 years were 40% less likely to have a live birth (OR 0.6, CI 0.4–0.8) and were almost three times more likely to experience cycle cancellation (OR 2.8, CI 1.5–5.3) and twice as likely to have an implantation failure (OR 2.0, CI 1.4–3.1) or pregnancy loss (OR 2.0, CI 1.2–3.4) than women who did not report exercise. In general, women who participated in cardiovascular exercise had a 30% lower chance of successful live birth (OR 0.7, CI 0.6–0.9) than women who reported no exercise.

CONCLUSION: Regular exercise before in vitro fertilization may negatively affect outcomes, especially in women who exercised 4 or more hours per week for 1–9 years and those who participated in cardiovascular exercise.
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LEVEL OF EVIDENCE: II-2

As the health benefits of exercise are increasingly recognized, more women are participating in a regular exercise program. The Centers for Disease Control and Prevention recommends 30 minutes or more of moderate-intensity physical activity on most, preferably all, days of the week.[1] Although exercise has been shown to have many health benefits, the relation between exercise and fertility is complex. As well demonstrated in female athletes, intense physical activity has been linked with anovulation and infertility. The spectrum of infertility resulting from exercise and low body mass index ranges from an inadequate luteal phase to anovulation and amenorrhea.[2] Conversely, evidence suggests that being overweight can cause ovulatory dysfunction and infertility.[2–4] In obese women, exercise leading to weight loss has been suggested to improve ovulation and subsequent fertility.[2,5,6]

Although exercise has been demonstrated to influence ovulation and fertility, the effects of exercise on in vitro fertilization (IVF) outcome are unknown. Exercise is a modifiable factor that could affect the success of IVF cycles. The purpose of this study is to examine this relation to help guide both physicians and patients.

MATERIALS AND METHODS

Approval for the study was obtained from the Partners Human Research Committee institutional review board, and all patients gave written informed consent.

The data for these analyses were collected from couples undergoing treatment for infertility from 1994–2003 at three IVF clinics in the greater Boston area as part of a collaborative prospective study sponsored by the National Institutes of Health. The

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primary aim of this National Institutes of Health study was to identify predictors of IVF outcomes, with exercise being one of the characteristics being evaluated. Couples consented to review of their medical records and completed a self-administered questionnaire before starting infertility treatment. All survey information was obtained before starting the IVF cycle and thus before knowledge of the IVF cycle outcome. Sixty-five percent of couples approached agreed to participate in the study. The couples included in this analysis were all undergoing their first cycle of IVF. The study questionnaire included questions about medical, environmental, and lifestyle factors, including the following questions about exercise 1) Do you regularly exercise? 2) If so, as an adult, how many years have you engaged in regular exercise? 3) How many hours per week do you exercise? 4) How many months per year do you exercise? and 5) What is your most frequent type of exercise? If women reported more than one type of exercise, only the primary type (the first one listed) was used in the analysis. The exercise information was assessed only before the IVF cycle; no information on exercise during the IVF cycle or during pregnancy was obtained.

Age, gravity, parity, and alcohol, tobacco, and caffeine use were also self-reported. Body mass index (BMI, kilograms per meter^2) was calculated based on self-reported height and weight. Cycle day three follicle stimulating hormone (FSH) and serum estradiol (E2) levels, gonadotropin dose, number of oocytes retrieved, and number of embryos transferred were recorded during the first cycle of IVF.

Three different groups were created based on the type of exercise women reported participating in most frequently. The "walking" group included those women who reported walking as their primary form of exercise. The "cardiovascular" group reported either jogging, running, aerobics, stair climbing, indoor rowing, elliptical treadmill, cross-country skiing, or bicycling as their primary exercise. Women who reported swimming, racquet sports, team sports (volleyball, soccer, softball, basketball), yoga, weight lifting, or martial arts were placed in a third exercise category called "other."

The outcomes reported included live birth after the IVF cycle and four potential points of failure during the IVF cycle. Each patient fell into one of these five categories. Patients experienced "cycle cancellation" if there was inadequate ovarian stimulation and oocyte retrieval was not performed, or if no oocytes were obtained during retrieval. "Failed fertilization" occurred if no embryos were available for transfer after insemination. If the patient underwent embryo transfer but never developed a chemical or clinical pregnancy, she experienced an "implantation failure." If the patient had evidence of implantation (defined as a positive hCG) but did not have a live birth, she was categorized as having had "pregnancy loss." These included women who had spontaneous abortions, therapeutic abortions, or ectopic pregnancies. The final group comprised patients who had a "live birth."

The women with live births were used as the controls for each of the failure case groups. This allowed for each point of failure group to have the same control group. Unconditional logistic regression was used to calculate the crude and multivariable odds ratios (ORs) and 95% confidence intervals (CIs) that are presented as estimates of relative risk associated with exercise.[7] In all analyses, the women who did not report any exercise were the referent group.

A multivariable OR for each main effect was calculated after adjusting for variables that were found to confound these crude relations. We considered all variables as potential confounders of the association of the exposure of interest with IVF outcomes if addition of that variable to the model changed the odds ratio by 10% or more.[8] If a factor was identified as a confounder of any estimated effect, it was kept in all models. Age, BMI, and year of the IVF cycle were identified as confounders and kept in all models. Gravity, parity, and use of caffeine, alcohol, and tobacco were all analyzed and not found to be confounders. Gonadotropin dose, number of oocytes retrieved, and number of embryos transferred were also analyzed and did not affect the primary results and were thus not included in the final analysis. Results were also analyzed adjusting for FSH on day three of the menstrual cycle.

The effect of exercise was an a priori hypothesis for this research study. The variables of interest included exercise frequency, duration, and type. No data mining beyond our a prior hypothesis was done in this study.

We conducted tests for trend in ordinal categorical exposures by creating an ordinal variable in which the median value or midpoint of each category was assigned to all participants in that group and then calculated a Wald statistic.[9] Test for trend across continuous variables was calculated using the Wald test.[9] Tests for heterogeneity were calculated with a Wald statistic from a multiplicative interaction term. Test of difference between exercise categories was calculated using analysis of variance. All reported P values are based on two-tailed tests, with $P \leq 0.05$ determining statistical significance.

In the absence of a linear trend across exercise durations, we calculated the effect of finely categorized exercise duration variables and then coalesced adjacent categories based on the observed effect estimates.[7] Given the observed threshold effect at 10 years of exercise and 4 hours of exercise, using arbitrary cut points (such as quartiles) would be inappropriate. Thus, we created the exercise duration categories presented in this paper.

RESULTS

A total of 2,232 couples undergoing their first cycle of IVF were enrolled in the study. Of these women, 1,368 reported that they engage in regular exercise, whereas 859 reported that they did not exercise. Of those 1,368 women who exercised regularly, 1,305 (95%), 1,334 (98%), and 1,348 (99%) women answered questions about years of exercise, months of exercise per year, and hours of exercise per week, respectively; 1,347 (98%) women answered questions about the type of exercise they performed. A documented menstrual cycle day 3 FSH level before their cycle of IVF was obtained in 1,581 women: 616 nonexercisers and 965 exercisers.

Of the women who reported regular exercise, the mean reported duration and frequency of exercise was 11.3 years, 10.8 months per year, and 4.3 hours per week. Walking was the most common form of exercise (n=568) (42%), followed by aerobics (n=307) (23%), jogging (n=199) (15%), and indoor cycling/rowing (n=104) (8%).

In the absence of a linear trend across exercise durations, we calculated the effect of finely categorized exercise duration variables and then coalesced adjacent categories based on the observed effect estimates. [7] Collapsing and combining these small increments of hours of exercise per week and years of exercise led to five exercise duration categories (Table 1). The demographics of these groups of women are shown in (Table 2); the groups differ with respect to age, parity, and alcohol intake.

Table 1. Exercise Duration Analytic Categories Among Women Undergoing Their First Cycle of In Vitro Fertilization

Exercise Duration Category	Hours per Week of Exercise	Years of Exercise	Number
No exercise	0	0	859
1	1–3	1–9	221
2	4 or more	1–9	230
3	1–3	10–30	352
4	4 or more	10–30	502

Among all women who reported regular exercise compared with those who did not, there was a 20% lower likelihood of successful live birth (OR 0.8, CI 0.7–1.0; P=.07), but this was not statistically significant. Regularly exercising women also had an increased risk of implantation failure (OR 1.3, CI 1.0–1.6; P=.04) (Table 3). Analysis of hours, months, and years of exercise as continuous variables did not reveal a linear relation between the amount of exercise and the success of IVF outcomes. Additionally, no significant linear association was identified by the use of a "lifetime exercise" variable, multiplying hours of exercise per week times 52 weeks times the number of reported years of exercise.

When compared with women who do not regularly exercise, women who exercised 4 or more hours per week for 1–9 years (exercise duration category 2) were 40% less likely to have a successful live birth after the first cycle of IVF (Table 3). These women were almost three times more likely to have a cycle cancellation (OR 2.8, CI 1.5–5.3) and twice as likely to experience implantation failure (OR 2.0, CI 1.4–3.1) or pregnancy loss (OR 2.0, CI 1.2–3.4) than women who did not report regular exercise. There was no difference in the rate of failed fertilization when comparing the women in exercise duration category 2 to women who did not exercise. The remaining exercise duration categories were not significantly different from the nonexercisers with respect to IVF outcomes. These results remained statistically significant after adjusting for FSH levels (data not shown).

For all analyses, the effect of BMI was closely analyzed. When patients were stratified by BMI using the World Health Organization BMI Categories for underweight (BMI<18.5), normal (BMI 18.5–24.9), overweight (BMI 25.0–29.9) and obese (BMI>30.0), no differences in the association between exercise and the IVF outcomes were noted (data not shown). Analysis by infertility diagnosis (ovulatory, male factor, tubal factor, uterine or cervical anomalies, endometriosis, and unexplained infertility) did not reveal any relation, confounding, or effect modification between infertility diagnosis and the effects of exercise on IVF outcomes (data not shown).

Further analyses examined the effect of the type of exercise on IVF outcomes. Three different groups were created based on the type of exercise women reported most frequently: "walking," "cardiovascular," or "other." There were statistically significant differences in age, gravity, parity, BMI, and use of alcohol and tobacco between the women in these

Table 2. Patient Characteristics by Exercise in General and by Exercise Duration Categories Among Women Undergoing Their First Cycle of In Vitro Fertilization

		Regular Exercise					
	No Exercise (n=859)	All Categories (n=1,305)	Category 1 1–3 h/wk for 1–9 y (n=221)	Category 2 4 h or more/wk for 1–9 y (n=230)	Category 3 1–3 h/wk for 10–30 y (n=352)	Category 4 4 h or more/wk for 10–30 y (n=502)	*P**
Age (y)	35 (29, 41)	35 (30, 41)	34 (30, 40)	33 (28, 40)	36 (31, 41)	36 (31, 41)	<.001
Gravidity	1 (0, 3)	0 (0, 3)	0 (0, 2)	0 (0, 3)	0 (0, 2)	0 (0, 3)	.26
Parity	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)	.02
BMI	23.4 (33.3, 19.7)	22.2 (19.5, 28.3)	22.7 (19.7, 27.7)	23.1 (19.6, 33.0)	22.0 (19.4, 28.3)	23.0 (19.4, 27.0)	.67
FSH	6.5 (3.9, 10.0)	6.9 (4.1, 10.6)	6.5 (3.9, 10.7)	6.9 (3.9, 10.4)	7.0 (4.1, 10.4)	6.8 (4.0, 10.7)	.09
Caffeine (mg/wk)	691 (0, 2877)	713 (0, 2562)	640 (0, 2562)	713 (0, 2877)	809 (0, 2240)	785 (0, 2476)	.12
Alcohol (drinks/wk)	0 (0, 6)	0 (0, 7)	0 (0, 7)	0 (0, 6)	1 (0, 8)	1 (0, 8)	<.001
Tobacco (pack-y)	0 (0, 11.3)	0 (0, 8.0)	0 (0, 9.5)	0 (0, 12.5)	0 (0, 4.5)	0 (0, 6.5)	.08

BMI, body mass index, kg/m^2; FSH, follicle stimulating hormone on day 3 of the menstrual cycle.
Data are median (range between 10th and 90th percentile).
* Test of difference between exercise categories calculated using analysis of variance.

groups (data not shown); confounders were adjusted for in all analyses.

Compared with those who do not exercise regularly, the likelihood of successful live birth for walkers in general was not different (OR 0.9, CI 0.7–1.2), whereas the likelihood of successful live birth for those undertaking cardiovascular exercise was 30% lower (OR 0.7, CI 0.6–0.9). However, among the exercise duration categories discussed in Table 1, focusing on category 2 (≥4 hours per week for 1–9 years) and category 3 (1–3 hours per week for 10–30 years) we observed exercise type specific associations (Table 4). Among the women who walked, those who had done so for 4 hours or more per week for 1–9 years (exercise duration category 2) were 50% less likely to have a successful live birth compared with women who did not regularly exercise. This was similar to the risk of IVF failure observed for exercisers overall in exercise duration category 2. Walking for 1–3 hours per week for 10–30 years (exercise duration category 3) was not associated with any change in the IVF outcomes.

Interestingly, the most detrimental effect was observed in cardiovascular exercisers, who had a 30% lower chance of successful pregnancy after their first cycle of IVF (OR 0.7, CI 0.6–0.9) than women who did not exercise. Among women who participated in cardiovascular exercise, exercise duration category 2 (≥4 hours per week for 1–9 years) was consistently associated with a significant decrease in IVF success. When compared with women who did not exercise, there was a 50% reduction in live births (OR 0.5, CI 0.3–0.8), with more than a five-fold increase in cycle cancellation (OR 5.1, CI 2.3–11.5) and an approximately a 2.5-fold increase in failed implantation (OR 2.6, CI 1.5–4.6) and pregnancy loss (OR 2.4, CI 1.1–4.9) (Table 4). These remained statistically significant after adjusting for FSH. Among the cardiovascular exercisers in exercise duration category 3 (1–3 hours per week for 10–30 years) there was less likelihood of a successful live birth (OR 0.6, CI 0.4–1.0, P=.04); however, this association was weaker than that seen in exercise duration category 2. This detrimental effect of cardiovascular exercise on IVF outcomes was not seen in exercise duration categories 1 and 4. The greatest effect was seen in moderate exercisers.

DISCUSSION

In this prospective study of women undergoing their first cycle of IVF, we observed a complex relation among exercise duration, exercise type, and IVF outcomes. Overall, exercise seems to be associated with reduced success after the first cycle of IVF. More specifically, exercising 4 hours or more per week for 1–9 years is associated with a decreased chance of a successful live birth. Cardiovascular exercise may have a more detrimental effect than walking.

Reproductive dysfunction associated with exercise seems to be related to alterations of the hypothalamic-pituitary axis. In some situations, such as intense exercise and decreased body mass, exercise can lead to anovulation and infertility.[10] On the other hand, in overweight patients with ovulatory dysfunction, exercise can lead to increased ovulation and improved fertility.[2,5,6]

There are several mechanisms by which exercise can lead to reproductive dysfunction. In women who participate in intense physical activities emphasizing leanness, suppression of pulsatile gonadotropin re-

Table 3. The Effect of Exercise on Successful Live Births and In Vitro Fertilization Points of Failure by Exercise Duration Category Among Women Undergoing Their First Cycle of In Vitro Fertilization

		Regular Exercise				
	No Exercise (n=859)	All Categories (n=1,305)	Category 1 1–3 h/wk for 1–9 y (n=221)	Category 2 4 h or more/wk for 1–9 y (n=230)	Category 3 1–3 h/wk for 10–30 y (n=352)	Category 4 4 h or more/wk for 10–30 y (n=502)
Cycle cancellation	1.0 (referent)	1.2 (0.8–1.8)	1.0 (0.5–1.9)	2.8 (1.5–5.3)*	1.1 (0.7–1.9)	0.7 (0.4–1.2)
Failed fertilization	1.0 (referent)	1.1 (0.7–1.6)	0.7 (0.4–1.6)	1.2 (0.6–2.6)	1.4 (0.8–2.4)	0.9 (0.5–1.5)
Implantation failure	1.0 (referent)	1.3 (1.0–1.6)†	1.0 (0.7–1.5)	2.0 (1.4–3.1)*	1.2 (0.9–1.7)	1.0 (0.8–1.3)
Pregnancy loss	1.0 (referent)	1.3 (1.0–1.8)	1.3 (0.8–2.2)	2.0 (1.2–3.4)*	1.3 (0.8–2.0)	0.9 (0.6–1.4)
Successful live birth	1.0 (referent)	0.8 (0.7–1.0)	0.9 (0.6–1.3)	0.6 (0.4–0.8)*	0.8 (0.6–1.1)	1.1 (0.8–1.4)

Data are odds ratio (95% confidence interval). Odds ratios are for multivariate logistic regression adjusting for age, body mass index and year of in vitro fertilization cycle.
* P value, Wald test less than .01.
† P value, Wald test .04.

Table 4. Likelihood of In Vitro Fertilization Outcomes by Exercise Category and Exercise Type Among Women Undergoing Their First Cycle of In Vitro Fertilization

Exercise Duration Category	IVF Cycle Outcome	No Exercise (n=859)	Walking (n=568)	Cardiovascular (n=661)
Regular exercise, all categories, any duration				
	Cycle cancellation	1.0 (referent)	0.9 (0.6–1.5)	1.5 (0.9–2.3)
	Failed fertilization	1.0 (referent)	0.9 (0.5–1.4)	1.4 (0.9–2.2)
	Implantation failure	1.0 (referent)	1.2 (0.9–1.5)	1.5 (1.1-1.9)*
	Pregnancy loss	1.0 (referent)	1.0 (0.7–1.5)	1.5 (1.0–2.2)†
	Successful live birth	1.0 (referent)	1.0 (0.7–1.2)	0.7 (0.6–0.9)*
Category 1: 1–3 h/wk, 1–9 y				
	Cycle cancellation	1.0 (referent)	1.2 (0.5–2.6)	1.4 (0.4–3.0)
	Failed fertilization	1.0 (referent)	0.3 (0.1–1.2)	1.2 (0.5–3.0)
	Implantation failure	1.0 (referent)	0.8 (0.5–1.3)	1.4 (0.8–2.4)
	Pregnancy loss	1.0 (referent)	0.9 (0.4–1.8)	1.8 (0.9–3.6)
	Successful live birth	1.0 (referent)	1.3 (0.8–2.1)	0.7 (0.4–1.1)
Category 2: 4 h or more/wk, 1–9 y				
	Cycle cancellation	1.0 (referent)	2.0 (0.8–5.5)	5.1 (2.3–11.5)*
	Failed fertilization	1.0 (referent)	1.7 (0.6–4.7)	1.2 (0.4–3.7)
	Implantation failure	1.0 (referent)	2.1 (1.2–3.9)‡	2.6 (1.5–4.6)*
	Pregnancy loss	1.0 (referent)	1.9 (0.9–4.0)	2.4 (1.1–4.9)†
	Successful live birth	1.0 (referent)	0.5 (0.3–0.9)†	0.5 (0.3–0.8)*
Category 3: 1–3 h/wk, 10–30 y				
	Cycle cancellation	1.0 (referent)	1.1 (0.5–2.2)	1.5 (0.7–3.1)
	Failed fertilization	1.0 (referent)	0.8 (0.3–1.8)	2.4 (1.2–4.8)
	Implantation failure	1.0 (referent)	1.1 (0.7–1.7)	1.6 (1.0–2.5)§
	Pregnancy loss	1.0 (referent)	1.1 (0.6–2.0)	1.3 (0.7–2.5)
	Successful live birth	1.0 (referent)	1.0 (0.7–1.5)	0.6 (0.4–1.0)§
Category 4: 4 h or more/wk, 10–30 y				
	Cycle cancellation	1.0 (referent)	0.5 (0.2–1.1)	0.9 (0.5–1.7)
	Failed fertilization	1.0 (referent)	1.1 (0.5–2.2)	0.7 (0.4–1.4)
	Implantation failure	1.0 (referent)	1.0 (0.7–1.5)	1.1 (0.7–1.5)
	Pregnancy loss	1.0 (referent)	0.8 (0.4–1.4)	1.2 (0.7–1.9)
	Successful live birth	1.0 (referent)	1.1 (0.8–1.6)	1.0 (0.7–1.4)

IVF, in vitro fertilization.
Data are odds ratio (95% confidence interval). Odds ratios are from multivariate logistic regression adjusting for age, body mass index and year of in vitro fertilization cycle.
* *P* value, Wald test less than .01.
† *P* value, Wald test .03.
‡ *P* value, Wald test .01.
§ *P* value, Wald test .04.

leasing hormone from the hypothalamus results in a hypoestrogenic state.[10–13] Sports that emphasize strength over leanness can be associated with menstrual irregularities,[10] mildly elevated luteinizing hormone levels, and mild hyperandrogenism rather than hypoestrogenism.[10,14,15] Intense exercisers have decreased levels of leptin, triiodothyronine (T3), and insulin.[10,12,16,17] Overall, the incidence of luteal phase defects, oligomenorrhea, anovulation, and subsequent infertility are significantly higher in athletes than nonathletes[10]; however, the mechanisms of the dysfunction may vary according to type of exercise.

Although IVF attempts to manipulate the hypothalamic-pituitary-ovarian axis, many other factors in the hormonal milieu can be influenced by exercise and may affect the success of the IVF cycle, as mentioned above. These factors may not be recognized, addressed or negated during an IVF cycle, and thus may still have an effect on overall IVF success.

We observed that in general, exercise could negatively affect the first cycle of IVF. However, there was no linear relation between the number of hours per week of exercise, number of years of exercise or lifetime exercise and IVF outcomes. When exercise duration categories were created, the negative effect of exercise (a statistically and clinically significant decrease in successful live births) is seen predominantly in women who reported exercising for 4 or more hours per week for 1–9 years (exercise duration category 2). The decrease in successful live births seen in exercise duration category 2 is supported by the increase in multiple points of failure: cycle cancellation, failed implantation, and pregnancy loss compared with women who did not exercise. Fertilization, which occurs in vitro in an artificial, standardized environment, is not affected by the exercise pattern of the women, suggesting that the detrimental effect on IVF outcomes is related to alterations in the woman's hormonal milieu or uterine environment.

Women in exercise duration category 2 were consistently noted to have poorer IVF outcomes. This finding persisted in women who reported either walking or cardiovascular as their primary exercise, although the effect was stronger in the cardiovascular group. It is possible that women in this category exercise long enough to alter their endogenous hormonal environment and affect the outcome of their first cycle of IVF.

In general, women in exercise duration category 1 (1–3 hours of exercise per week for 1–9 years) or exercise duration category 3 (1–3 hours of exercise per week for 10–30 years) did not have less successful IVF outcomes than women who do not exercise. One possible explanation is that women who exercise for such a short duration each week may not change their hormonal environment enough to affect the outcome of their first IVF cycle. The women in exercise duration category 4 (≥4 hours per week for 10–30 years) did not demonstrate any differences in their IVF outcomes when compared with women who do not exercise. It is possible that the women who exercised at this intensity for more than 10 years have achieved an equilibrium or created a different hormonal environment from those women who exercise for the same number of hours per week for less than 10 years. Our results were unexpected. Although we cannot explain the pathophysiology of these findings with the information obtained in out study, we provide one possible explanation above.

Cardiovascular exercise in general was correlated with a statistically significant decrease in IVF success, whereas walking was not. This implies that walking may not be an intense enough exercise to alter the environment to affect the IVF outcomes negatively.

There is increased risk for ovulatory infertility in both underweight patients (BMI<20) and overweight patients (BMI>24).[2,3] Among overweight patients with ovulatory dysfunction, exercise can lead to increased ovulation and improved fertility.[2,5,6] However, we did not observe any difference in the relation between exercise and IVF outcomes among the different BMI groups.

There are several limitations of this study. Patients completed the survey and reported their exercise history before the start of the IVF cycle. Although there may be inaccuracies in the self-reporting of exercise, any differential bias should be negated, given that the patients had not yet undergone IVF and thus did not know their outcome. Because of the prospective nature of the data collection before the IVF cycle, recall bias is eliminated. The self-reported exercise inaccuracies should not be different in those patients with successful IVF outcomes and those with unsuccessful cycle outcomes; the exercise information was gathered before knowledge of the cycle outcome. Furthermore, we have information only about general exercise patterns before starting the first cycle of IVF. Patients reported exercise patterns over years (hours per week and years they have been exercising); the exact exercise pattern, types of exercise performed, and intensity of exercise most likely. Furthermore, patients may have altered their exercise patterns when they started trying to conceive, before their referral for IVF. We did not have information about exercise patterns during the IVF cycle which could also affect outcomes.

In general, the type, intensity, frequency, and duration of exercise are difficult to quantify. Although patients did report average hours of exercise per week, we do not have information about the length, intensity, or frequency of each individual exercise session. For example, 4 hours of reported exercise per week could be two 2-hour sessions or eight half-hour sessions. Thus, the effect of such differences could not be studied. When creating exercise variables, we attempted to report standardized metabolic equivalents, but without more specific information on intensity of the physical activity, this could not be done with accuracy. In creation of the general exercise type categories (ie, "walking," cardiovascular," and "other") we initially attempted to follow the Centers for Disease Control and Prevention and American College of Sports Medicine categorization of physical activity. However, these systems are based on metabolic equivalents that could not be accurately defined with the survey information obtained. When trying to examine very specific exercise categories separately (such as stretching and strengthening exercises) the numbers were too small to yield any meaningful results. This led to the development of the final exercise type categories presented, with the lumping of "cardiovascular" and "other" activities.

The survey completion rate was 65%. Typically 70% is the desired completion rate in epidemiologic studies. Given the stress than most couples are under by the time they reach IVF, we feel that this is an excellent response rate.

Last, exercise is a lifestyle factor with associated behaviors that may be potential confounders. The analysis in this study was designed to address some of these factors by adjusting for BMI and use of alcohol, caffeine, and tobacco. However, there are certainly other confounders that we could not identify or account for, such as diet and level of job stress.

Despite these limitations, this large, prospective study demonstrates that certain types of exercise patterns may affect the success of IVF. Although exercise has many known health benefits, it does not seem to contribute to successful IVF outcomes. However, our findings are not strong enough to encourage women to abandon exercise and embrace a sedentary lifestyle. Future studies are needed to clarify the relation between exercise and IVF outcomes. As with all studies, these findings should be replicated before making any definitive clinical recommendations.

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